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Cystatin C in addition to creatinine for better assessment of glomerular renal function decline in people with HIV receiving antiretroviral therapy

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Abstract

Objective:

To compare the estimated glomerular filtration rate (eGFR) using the creatinine equation (eGFR_{creat}) or the cystatin C equation (eGFR_{cys}) in people with HIV (PWH) under antiretroviral drugs. We specifically included patients with an eGFR_{creat} around 60 ml/min per 1.73 m² to evaluate agreement on stage 2 and 3 chronic kidney disease (CKD) classification.

Design:

eGFR_{creat}, eGFR_{cys} and resulting CKD staging were determined in 262 consecutive patients with HIV-1 (PWH) with a suppressed viral load (<200 copies/ml) under antiretroviral drugs and having impaired renal function (eGFR_{creat} between 45 and 80 ml/min per 1.73 m²). Antiretroviral drugs regimens were classified into eight groups: cobicistat (COBI)+elvitegravir (EVG), ritonavir (RTV)+protease inhibitor, dolutegravir (DTG), DTG+rilpivirine (RPV), RPV, raltegravir (RAL), bictegravir (BIC), and other antiretroviral drugs.

Results:

Mean eGFR_{cys} was higher than mean eGFR_{creat} (77.7 ± 0.5 vs. 67.9 ± 7.9 ml/min per 1.73 m², $P < 0.0001$). The differences were significant in five treatment groups with COBI/EVG; DTG; DTG+RPV; RPV; RAL. CKD classification was modified for 51% of patients when using eGFR_{cys} instead of eGFR_{creat}, with reclassification to less severe stages in 37% and worse stages in 14%.

Conclusion:

This study highlighted significant differences in eGFR depending on the renal marker used in PWH, having a significant impact on CKD classification. eGFR_{cys} should be an additive tool for patients having eGFR_{creat} around 60 ml/min per 1.73 m² for better identification of renal impairment.

Introduction

Evaluation of chronic kidney disease (CKD) is done in clinical practice by measuring plasma or serum creatinine levels to estimate glomerular filtration rate (eGFR) using the Chronic Kidney Disease - Epidemiology Collaboration (CKD-EPI) equation [1]. Creatinine is considered a clinically relevant endogenous hallmark of kidney function because it is mostly excreted by glomerular filtration and is not concerned by tubular reabsorption. However, creatinine can also be secreted by proximal tubular cells (PTC) at low rates in physiological states [2] but at increased rates in kidney failure [3]. This secretion is known to be inhibited during the use of xenobiotics [4]. For instance, cimetidine [5], trimethoprim [6], and pyrimethamine [7] are widely known as inhibitors of creatinine secretion (ICS), an effect that was also described more recently with the use of some antiretroviral drugs. Indeed, dolutegravir (DTG) and rilpivirine (RPV) have been identified as inhibitors of the organic cation transporter 2 (OCT-2) whereas ritonavir (RTV) and cobicistat (COBI) inhibit the multidrug and toxin extrusion 1 (MATE-1) transporter (Supplemental Figure 1, <http://links.lww.com/QAD/C718>) [8–10]. Other integrase inhibitors have been suspected as ICS but with debating involvement such as raltegravir (RAL) [11–12] or bictegravir (BIC) [13]. As a result, inhibition of transporters can lead to an elevation of plasma creatinine unrelated to glomerular function decline, causing errors in the staging of CKD. This misclassification could impact the management of people with HIV (PWH), depending on their antiretroviral drugs. Hence, another biomarker of kidney function that is plasma or serum cystatin C could have a great interest in this population.

Cystatin C is a small protein produced physiologically by all human nucleated cells that is fully filtered by renal glomeruli and also fully reabsorbed by PTC in which it is catabolized [14]. Unlike creatinine, plasma or serum cystatin C concentration is independent of muscle mass and tubular secretion and is often proposed as an alternative endogenous kidney function marker to creatinine [15]. For many years, the CKD-EPI cystatin C equation has been developed for estimation of GFR [16], and eGFR_{cys} is now recommended in addition to eGFR_{creat} in specific populations with large physiological variations of plasma creatinine levels, for instance, in paediatrics [17]. Moreover, since 2012, The Kidney Disease: Improving Global Outcome (KDIGO) recommendation suggests the use of cystatin C to confirm an eGFR_{creat} between 45 and 59 ml/min per 1.73m² (CKD stage G3a), in patients without albuminuria or other manifestations of kidney damage [18]. A suitable application of cystatin C measurement could also be in PWH receiving specific antiretroviral drugs, known for being ICS. Indeed, initiation of DTG leads to an increase in creatinine levels and a decrease of eGFR_{creat} without effect on cystatin C levels and eGFR_{cys} [19]. A previous study demonstrated in patients receiving DTG that eGFR_{cys} is more accurate than eGFR_{creat} when compared with inulin clearance [20]. To our knowledge, exploring the risk of misclassification of PWH on eGFR stages G2–G3a because of antiretroviral drugs has never been studied. With the continuous increase in life expectancy [21] and the long-term use of antiretroviral drugs, PWH will be more concerned by CKD than they were before [22]. Prevalence of eGFR less than 60 ml/min per 1.73m² in PWH was reported as 5% in 2004 compared with 30% in 2014 in the same cohort with an increase concerning experienced antiretroviral drugs-HIV but even more for newly treated patients and naive patients. These data illustrated the complex interactions between several factors (lifestyle, HIV per se in relation to viral load, antiretroviral drug exposure susceptible to induce tubular dysfunction including Fanconi syndrome) and renal function evolution [23].

The objective of this study was to compare the eGFR using the creatinine equation to eGFR using the cystatin C equation in PWH on antiretroviral drugs and with an eGFR_{creat} around 60 ml/min per 1.73m² to evaluate agreement on CKD classification.

Material and methods

Design

During 4 months (June to September 2019), all adults living with HIV seen at the Montpellier University Hospital Infectious diseases outpatient clinic and having an eGFR_{creat} between 45 and 80 ml/min per 1.73m² were included. All patients had measurements of plasma creatinine, cystatin C, CD4⁺ lymphocyte cell count, and HIV viral load. Clinical data, detailed antiretroviral drugs history and, if present, albuminuria/creatininuria ratio (ACR) were collected from medical records. Exclusion criteria were: absence of antiretroviral drugs, concomitant treatment with DTG and RTV, treatment with trimethoprim within 6 months prior to the inclusion, and a viral load greater than 200 copies/ml. This observational study was approved by the local ethic committee and was declared under the number DC-C-2012-1579.

Patients were classified according to their antiretroviral drugs into eight groups: receiving COBI/EVG (n=29), RTV/PI (n=22), DTG (n=497), DTG and RPV (n=16), RPV (n=32), RAL (n=25), BIC (n=19), and receiving other drugs (efavirenz, nevirapine, etravirine, n=22).

Preanalytical and analytical steps

Lithium Heparin tube was collected from biological quarterly follow-up, then centrifuged 10 min at 2000g. Plasma creatinine was measured by enzymatic method on COBAS 8000 (Roche, Meylan, France). Plasma cystatin C was measured by Particle-Enhanced Turbidimetric Immunoassay (PETIA) using Diasys Reagent [24] on a BS 480 apparatus (Mindray, Shenzhen, China), eGFR was determined by CKD-EPI equations, using 2021 version for creatinine [1] and 2012 version for cystatin C [16]. Classification of CKD was based on the KDIGO definition [25].

Statistical analysis

Passing–Bablok regression analysis was used to compare the eGFR_{creat} to eGFR_{cys}. The scatter of differences was visualized through Bland–Altman plots [26]. Kolgomorov–Smirnov test was used to assess normality.

The difference between eGFR was analysed by Student's t test. Chi-square and MacNemar's test were performed to compare qualitative data. For all comparisons, alpha significance level was set at 5% and a P value under 0.05 was considered statistically significant. The concordance between CKD classification of patients using creatinine and cystatin C was assessed using weighted Cohen's k test with a value less than 0.2 indicating poor agreement, value greater than 0.8 indicating very good agreement. Statistical analyses were performed using XLSTAT software, version 2016.06.35661 (New York, USA) and R software, version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria).

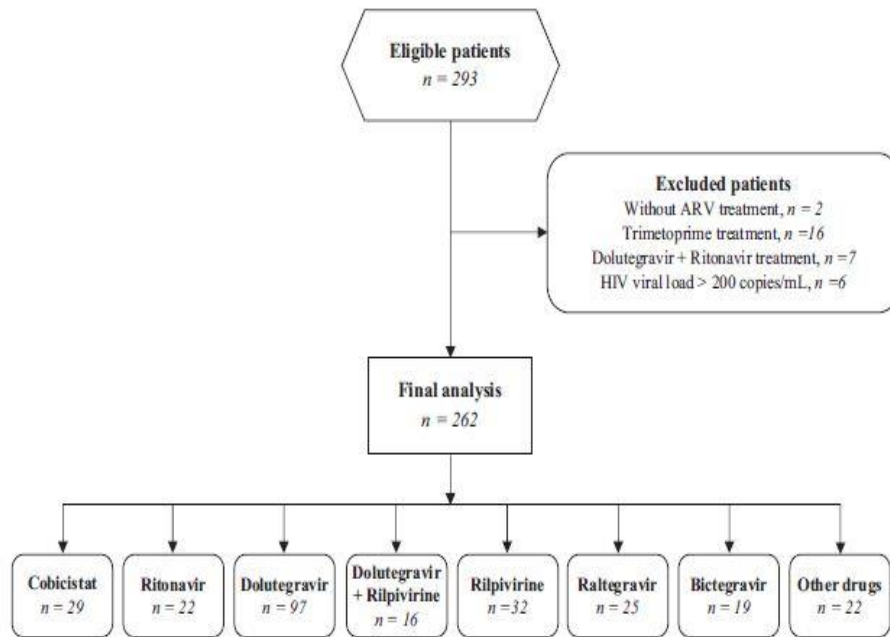


Fig. 1. Flow-chart diagram of the studied patients and treatment groups.

Results

Population

Recruitment for the study is detailed in Fig. 1. Among 293 eligible patients, 262 were included (Table 1). The mean age of the whole population was 58.3 years, 72.5% were men. Cardiovascular comorbidities were highly prevalent, hypertension being the most prevalent among them. On the virological side, patients were treated with the present antiretroviral drugs regimen for an average of 3.7 years, most of them having an undetectable viral load and a high CD4⁺ cell count. No correlation between CD4⁺ cell count and cystatin C levels was observed (Pearson's coefficient, $r=0.049$, $P=0.420$). Three quarters of patients were exposed to recognized ICS through OCT-2 ($n=145$) or MATE-1 ($n=51$). Nucleoside/ nucleotide reverse transcriptase inhibitors (NRTIs) used were mainly emtricitabine, lamivudine, abacavir, and tenofovir.

Correlation between estimated glomerular filtration rate with creatinine and estimated glomerular filtration rate with cystatin C

Regression between eGFR_{creat} and eGFR_{cys} gave the following equation: $y=0.98x + 11$ (Pearson's coefficient, $R=0.378$, $P<0.0001$) (Supplemental Figure 2, <http://links.lww.com/QAD/C718>). Bland-Altman's plot (Fig. 2), showed a median bias at 9.3 ml/min per 1.73m² and a positive linear relationship between mean of methods and their difference. We identified five major outliers: four with higher eGFR using cystatin C leading

to a difference $eGFR_{cys} - eGFR_{creat}$ of more than 50 ml/min per $1.73m^2$ (n=3 in DTG group, n=1 in COBI group) and one outlier in the opposite way leading to an $eGFR_{cys}$ inferior by 39 ml/min per $1.73m^2$ compared with $eGFR_{creat}$ for a patient in the RPV group having hepatic cirrhosis (creatinine: 100mmol/l, cystatin C=1.9mg/l, urea=4.7mmol/l, C-reactive protein=5.1mg/l).

Comparison between estimated glomerular filtration rates

$eGFR_{cys}$ and $eGFR_{creat}$ in the whole population and the eight treatment groups are presented in Supplementary Table 1, <http://links.lww.com/QAD/C718>. No difference between $eGFR_{cys}$ nor $eGFR_{creat}$ according to antiretroviral drugs duration was observed (Supplementary Fig. 3, <http://links.lww.com/QAD/C718>). There was no significant difference in terms of BMI and age between the eight groups. In addition, no difference in $eGFR_{creat}$ according to the antiretroviral drugs group was observed, nor for $eGFR_{cys}$. However, as summarized in Fig. 3, mean $eGFR_{cys}$ was significantly higher than mean $eGFR_{creat}$ in the whole population and for five groups (COBI, $P < 0.01$, DTG, $P < 0.001$, DTG+RPV, $P < 0.01$, RPV, $P < 0.05$, RAL, $P < 0.05$). No statistical difference was observed for the three other groups (RTV, $P = 0.104$, BIC, $P = 0.089$, others, $P = 0.131$). Mean difference ranged between 5.5 ± 22.4 (others) to 14 ± 19 (DTG) ml/min per $1.73m^2$.

Estimated glomerular filtration rate classification

In the whole population, 18% of patients had $eGFR$ less than 60 ml/min per $1.73m^2$ with the creatinine equation compared with 17.2% for cystatin equation. Only 49% of patients remained in the same $eGFR$ classification with both renal markers while 37% were reclassified in less severe stages with cystatin C equation and 14% had an aggravated stage with cystatin C equation (Fig. 4). A poor agreement between $eGFR_{creat}$ and $eGFR_{cys}$ was observed (weighted kappa, $wk = 0.100$).

Among patients with worsened $eGFR$ stage with $eGFR_{cys}$, 45.2% exhibited ACR greater than 3mg/mmol compared with 14.1% for the other patients ($P < 0.001$) suggesting a chronic glomerular injury. Those patients were more likely to have BMI less than 18.5 (20 vs. 4.8% $P < 0.011$), and had increased levels of blood urea nitrogen (7.3 vs. 6.4mmol/l, $P < 0.05$), supporting a worsened glomerular function evidenced by lower $eGFR_{cys}$ in comparison with $eGFR_{creat}$.

Table 1. General characteristics, comorbidities and virological parameters of the population.

Criteria	Value	
Mean age (years, \pm SD (min-max))	58.3	\pm 10.7 (29.5–87.3)
Gender (M%)	72.5	
BMI (kg/m ²)		
<18.5 (%)	6.9	
18.5–24.9 (%)	50.3	
24.9–30 (%)	33.3	
>30 (%)	9	
Hypertension treatment (%)	29.1	
Diabetes treatment (%)	6.6	
Hypercholesterolemia treatment (%)	19.7	
History of myocardial infarction (%)	7	
Current smoker (%)	16.9	
Thyroid hormone replacement therapy (%)	5.3	
Corticosteroid medication (%)	3.5	
Current or past coinfection		
HBV (%)	16.8	
HCV (%)	4.2	
CD4 ⁺ cell count (cells/ μ l)		
>500 (%)	73.7	
200–500 (%)	23.7	
<200 (%)	2.7	
HIV viral load <50 copies/ml (%)	98.9	
Mean duration of current ART regimen [years, \pm SD (min-max)]	3.7	\pm 3.3 (0.1–17.7)
Inhibition of creatinine secretion (%)		
Through OCT-2 (DTG, RPV)	55.3	
Through MATE-1 (COB, RTV)	19.5	
Debating ICS (RAL, BIC)	16.4	
No ICS (efavirenz, nevirapine, etravirine)	8.4	
NRTI (%)		
Emtricitabine	49.1	
Lamivudine	36.7	
Abacavir	28.7	
Tenofovir alafenamide	16.7	
Tenofovir disoproxil	10.5	
Zidovudine	0.36	
No NRTI used	14.2	

BIC, bicitgravir; COBI, cobicistat; DTG, dolutegravir; ICS, inhibitors of creatinine secretion; NRTI, nucleotide reverse transcriptase inhibitor; RAL, raltegravir; RPV, rilpivirine; RTV, ritonavir; SD, standard deviation.

Discussion

This study highlighted significant differences between eGFR using creatinine or cystatin C around the clinical cut-off of 60 ml/min per 1.73m² in PWH, especially for those treated by COBI, DTG, RPV, or RAL. These discrepancies led to a poor agreement in CKD classification, which should be critical for referring the patient to a nephrologist in adequate cases. Early detection of patients with impaired eGFR will allow a better modulation of antiretroviral drug therapy and initiation of nephroprotective management.

It is well recognized that creatinine secretion or muscle mass variation could modify creatinine level independently of the glomerular function and, therefore, in paediatrics or in extreme BMI, cystatin C in plasma, or serum appears as an alternative endogenous kidney function marker [17]. However, several biases were also reported for cystatin C, which may affect CKD assessment. For instance, increased levels are encountered in the general population in hyperthyroidism or under glucocorticoids use [27,28]. In PWH, increased levels had been reported in cases of uncontrolled viral load [29]. Otherwise, decreased levels occur notably in hypothyroidism and in several cancers [27,30,31].

The present study focused on PWH treated with antiretroviral drugs aged around 60 (+/-10.7) years without significant difference between groups for age and BMI, which could have impacted creatinine levels [32] and with suppressed HIV viral load to avoid impact on cystatin C [29]. As a current hypothesis, overestimation of plasma creatinine because of ICS exposure would erroneously decrease the eGFR. antiretroviral drugs such as DTG,RPV, COBI, and RTV are reported as effective ICS through interaction with PTC transporters leading to a bias in the estimation of kidney function [8–10] with a potential additive effect when using multiple ICS in the antiretroviral drug strategy [33]. Indeed, after initiation of darunavir/COBI in combination with DTG and/or RPV, a decrease of eGFR_{creat} more than 15 ml/min per 1.73m² could be observed [33]. In our study using cystatin C equation for eGFR determination is mainly associated with higher eGFR compared to creatinine CKD-EPI equation. In the whole population, average eGFR_{cys} was enhanced by 9.3 ml/min per 1.73m² compared with eGFR_{creat}.

Although an artefactual decrease of eGFR was expected only in groups receiving antiretroviral drugs with ICS effect, we observed a trend to a similar pattern for all groups but with a statistical significance for well-known ICS (DTG, DTG+RPV, RPV). The higher difference was 14+/-19 ml/min per 1.73m² for DTG group, which can be considered clinically relevant, especially around the critical value of 60 ml/min per 1.73m². We also found a difference between eGFRs for RAL, in agreement with the report of moderate creatinine increase after initiation of RAL [11]. It could not be excluded that significance was not reached in RTV and BIC groups because of the low number of patients.

Regression analysis between eGFR_{cys} and eGFR_{creat} showed a poor correlation that affects the eGFR classification. Indeed, almost half of patients had a change of eGFR classification although the proportion of patients with eGFR less than 60 ml/min per 1.73m² was similar with creatine or cystatin equation (18 vs. 17.2%). According to the KDIGO, an overall trend to a CKD reclassification towards less severe stage with cystatin C equation compared with creatinine equation was observed for 37% of the whole population. An unnecessary renal alert could be done for 31 patients on G3 with eGFR_{creat} moving to G2 or G1 stage with eGFR_{cys}. By contrast and unexpectedly, 14% of patients had worsened stage when cystatin C equation was used. These patients were more likely to have albuminuria and higher urea strongly suggesting a decline of glomerular function or having a low BMI suggesting an overestimation of eGFR_{creat}. In these cases, potential under diagnosis of CKD with eGFR_{creat} could delay the referee of patients to nephrologists and thus the nephroprotective measures to limit CKD progression. In this context, assessment of proteinuria or albuminuria in PWH biological follow-up is of great interest. Indeed, proteinuria is a prevalent condition in PWH under antiretroviral drugs [34] and is associated with renal prognostic [35]. By contrast, the usefulness of other urinary biomarkers to assess the tubular function such as urinary cystatin C remains controversial [36, 37]. It has been recently reported that serum cystatin C and ACR are predictive of mortality or cardiovascular events in PWH [38].

Therefore, assessment of proteinuria, albuminuria is important in the follow-up of PWH in addition to eGFR.

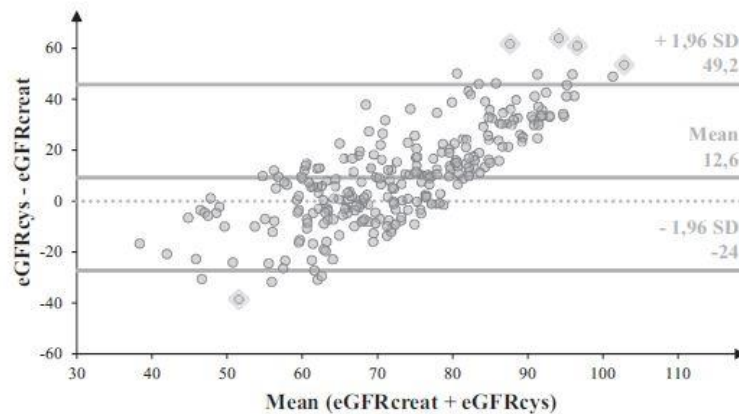


Fig. 2. Bland–Altman's plot between eGFR_{creat} and eGFR_{cys}. x-axis represents mean of eGFR_{creat} and eGFR_{cys}. y-axis represents the difference between eGFR_{creat} and eGFR_{cys}. Both values are in ml/min per 1.73m². Major outliers are highlighted by gray shadow.

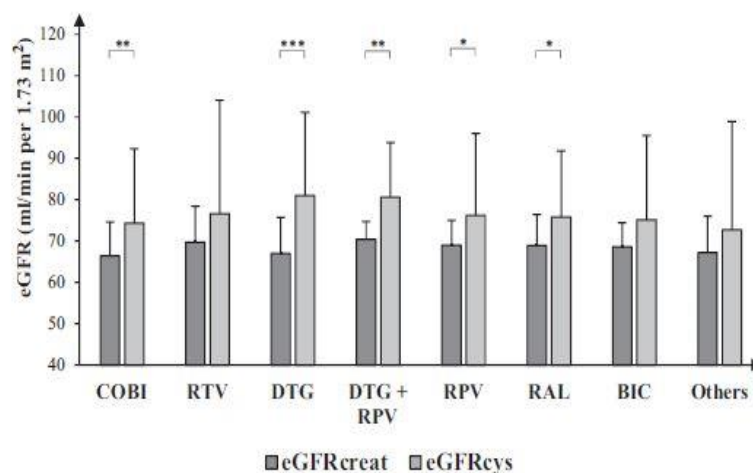


Fig. 3. Comparison of mean estimated glomerular filtration rates (ml/min per 1.73 m²) obtained by using creatinine (eGFR_{creat}) or cystatin C (eGFR_{cys}), in the different groups. The black error bars represent standard deviation for each value. **P* < 0.05, ***P* < 0.01, ****P* < 0.001.

		eGFR stage, eGFR _{cys}			
		G1	G2	G3a	G3b
eGFR stage, eGFR _{creat}	G1	0	0	0	0
	G2	65 (24.8)	121 (46.2)	23 (8.8)	6 (2.3)
	G3a	3 (1.1)	28 (10.7)	8 (3.1)	8 (3.1)
	G3b	0	0	0	0

$\kappa = 0,007$ (95%IC = -0.060; 0.075), $w\kappa = 0,100$

n = 262

Fig. 4. Evaluation of the concordance between chronic kidney disease classification using creatinine and cystatin C (n, (%)) by Cohen's κ -test in the whole population. Beneficial reclassification with eGFR_{cys} was underlined in mild gray and worsen reclassification in dark gray.

Taken together, these discrepancies in CKD classification pinpointed that each renal marker has some limits and illustrated the complexity to evaluate the renal function in PWH under antiretroviral drugs. Previous studies showed that cystatin C does not outperform creatinine when compared with measured GFR by iohexol [39, 40]. However, these studies focused on patients with measured GFR around 90 ml/min per 1.73m² (95+/-24 and 87+/-26 ml/min per 1.73m² respectively), whereas our study focused on patients with eGFR around 60 ml/min per 1.73m² at the limit between G3a and G2 stages. On the other hand, another study reported that eGFR_{cys} appears more precise than eGFR_{creat} when compared with measured GFR with inulin clearance [20]. In agreement with this data, other studies reported an interest in cystatin C use in PWH treated with DTG, RPV, or COBI [41, 42]. Combined equation using creatinine and cystatin C (eGFR_{cyscreat}) has been shown to be useful in the general population with a stage G2 to G3a [16]. Recently, Lucas et al. have suggested that eGFR_{cyscreat} could be an interesting alternative in PWH [43]. However, we did not evaluate the combined equation considering that bias of creatinine was included in eGFR_{cyscreat}.

Thus, a rational strategy could be to implement eGFR_{cys} in addition to eGFR_{creat} in the follow-up of PWH with eGFR_{creat} around 60+/-15 ml/min per 1.73m² to infirm or confirm a decline of glomerular function. A parallel decrease of both eGFR on two measurements obtained at least 3 months apart, in the absence of evident bias of each marker should be considered as renal impairment.

This study has some limitations: first, it is a monocentric observational study potentially not representative of the whole population living with HIV. Second, it is a cross-sectional study, biological assessments were carried out from only one blood sample. Third, the number of patients in each antiretroviral drug subgroup limits the potency of statistical analysis. Fourth, gold-standard GFR measurement is not available. Strength of the study is based on the selected population with an eGFR_{creat} around 60ml/min per 1.73m² including G2 and G3a eGFR stages.

In conclusion, a poor agreement was obtained in eGFR stage classification using CKD-EPI equations based on creatinine versus cystatin C levels in PWH having an eGFR_{creat} around 60 ml/min per 1.73m². Some antiretroviral drugs known as ICS could explain only a part of these discrepancies. This study highlighted the complexity of glomerular renal function assessment in PWH receiving antiretroviral drugs and suggest to add eGFR_{cys} for better identification of patients in need of a nephrology referral.

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Conflicts of interest

There are no conflicts of interest.

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